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Best evidence topic

What is the best neoadjuvant regimen prior to oesophagectomy: Chemotherapy or chemoradiotherapy?

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ABSTRACT

A best evidence topic in upper gastrointestinal surgery was written according to a structured protocol. The question addressed was whether neoadjuvant chemotherapy (CT) or chemoradiotherapy (CRT) in patients with resectable oesophageal cancer is associated with the best clinical outcome. 1115 papers were found of which 5 papers were identified to answer the clinical question including 2 randomised controlled trials (level II), 2 prospective series (level II) and one retrospective study (level III). The evidence suggests CRT significantly increases the pathological complete response rate and in some studies this is associated with a significant survival advantage. This is at the cost of an increase in peri-operative morbidity and mortality. However, both randomised studies were significantly underpowered and no standard CT or CRT regimen appears to have been used in any study. Therefore, controversy still exists as to whether neoadjuvant CT or CRT is more beneficial and this has lead to variation in practice around the globe. Two randomised controlled trials are currently underway which will hopefully answer this important clinical question.

1. Introduction

Based on the clinical scenario presented below, a search was constructed according to a structured protocol as described in a recent 'best evidence' paper in the *International Journal of Surgery*.[1] Best BETs are designed to answer clinically relevant questions and allow clinicians to rapidly review the literature on a defined topic. Although a meta-analysis comparing neoadjuvant chemotherapy (CT) and chemoradiotherapy (CRT) has been conducted in oesophageal cancer,[2] it only included randomised studies and assessed the impact of post-operative mortality and survival only. Here we review all the pertinent literature which directly compares CT with CRT and assess other important clinical factors, such as toxicity and the differences in pathological complete response rate and margin status.

2. Clinical scenario

You are in the outpatient clinic with a 75-year-old male patient who has recently been diagnosed with oesophageal cancer. His computed tomogram, positron emission tomography (PET) and endoscopic ultrasound show a potentially resectable distal adenocarcinoma (T3, N1, M0). His general health is good and he is suitable for neoadjuvant therapy followed by oesophagectomy. He has been reading about the oncological options on the internet and asks whether he will be receiving neoadjuvant CT or neoadjuvant CRT prior to his surgery. You decide to check the recent literature to determine which neoadjuvant therapy prior to oesophagectomy for cancer offers the best clinical outcomes: CRT or CT?

3. Three-part question

In patients undergoing neoadjuvant treatment prior to oesophagectomy, does neoadjuvant CT or neoadjuvant CRT improve outcomes?

4. Search strategy

A Medline search from 1946 to 2013 using the Ovid interface for the terms: (oesophagectomy [All Fields] OR oesophageal neoplasia [All fields]) AND (neoadjuvant therapy [All Fields] OR neoadjuvant chemotherapy OR neoadjuvant chemoradiotherapy OR pre-operative chemotherapy OR pre-operative chemoradiotherapy) was performed. Results were limited to papers published in the English language and those relating to Humans. Only papers which

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Table 1
Best evidence papers.

Author, date and country	Patient group	Study type (level of evidence)	Regimen	Key outcomes	Comments
Stahl, 2009, Germany[2]	119 patients with cT3–4NxM0 AC of lower oesophagus or gastric cardia CT ($n = 59$) CRT ($n = 60$)	Unblinded, prospectively randomised phase III trial (II)	CT: 15 weeks (w) of cisplatin, fluorouracil (5-FU) + leucovorin CRT: same CT for 12 w followed by 3 w 30 Gy RT in 15 fractions + cisplatin + etoposide	OS: 21.1 months CT, 33.1 months CRT. 3 year survival 27.7% for CT, 47.4% after CRT ($p = 0.07$) Toxicity: No difference Path CR: 15.6% after CRT, 2% after CT ($p = 0.03$) Hospital Mortality: 3.8% after CT and 10% after CRT ($p = 0.26$) 3 year DFS: 59.0% for CT vs. 76.5% for CRT ($p = 0.06$)	Aimed for 354 patients but finished prematurely due to low accrual. Power to detect a 10% difference only 40%. 52 in CT and 49 pts in CRT group underwent surgery. Reasons for no surgery were toxicity chemo (2 vs. 2), tumour progression (3 v 5), unfit (0 v 1) and other (2 v 3), for CT vs. CRT groups respectively. Complete resection was 69.5% in CT group vs. 72% for CRT group. Median follow-up 45.6 months. Low dose of radiotherapy used (30 Gy). Non-standard chemotherapy regime.
Burmeister, 2011, Australia[3]	75 patients with cT2–3 cN0–1 AC of the thoracic oesophagus or gastro-oesophageal junction CT ($n = 36$) CRT ($n = 39$)	Unblinded, prospectively randomised phase II trial (II)	CT: 2 cycles cisplatin 80 mg/m^2 + 96 h infusion of 5-FU CRT: same dose of cisplatin, but 1000 mg/m^2/d 5-FU in the 1st cycle and 800 mg/m^2/d in the 2nd cycle Concurrent with the 2nd cycle of CT 35 Gy of RT in 15 fractions over 3 w	OS: Median 29 months after CT and 32 months after CRT ($p = 0.83$) Toxicity: No difference Path CR: 13% after CRT, 0% after CT ($p = 0.02$) R0 resection: R1 rate was 0% after CRT but 11% after CT ($p = 0.04$) Progression Free Survival: Median 14 months after CT and 26 months after CRT ($p = 0.37$)	Surgery was standardised. Median follow-up 94 months (range 43–112 months). Aimed for 100 patients, but recruitment stopped after 75 patients as there were problems with waiting list for RT. Underpowered.
Swisher, 2010, USA[4]	157 patients with cT1–3 cN0–1 AC or SCC of the oesophagus entered into sequential trials between 1990 and 2000 CT ($n = 76$) CRT ($n = 81$)	Unblinded, prospectively randomised phase II/III trial (II)	CT ($n = 44$) 3 cycles cisplatin 100 mg/m^2 + 5-FU 1000 mg/m^2, (positive response to CT: also given post-operative Cisplatin + 5-FU) CT ($n = 32$) 3–5 cycles of cisplatin (3 × 30 mg/m^2), 5-FU (3 × 1250 mg/m^2) + arabinoside (2 × 1800 mg/m^2) (if given <5 cycles, remainder was given post-operatively if evidence of response) CRT: ($n = 38$) 2 cycles of 5-FU, cisplatin + paclitaxel followed by a combination of 45 Gy of RT in 25 Gy fractions + Cisplatin + 5-FU CRT: ($n = 43$) 2 cycles of CPT-11 + cisplatin, followed by 45 Gy of RT in 25 Gy fractions + Paclitaxel + 5-FU	OS: Median survival 32 months for CRT vs. 18 months for CT ($p = 0.05$) 5 year survival 36% for CRT, 21% for CT ($p = 0.04$) Toxicity: Higher rates of neutropaenic sepsis, nausea and vomiting, diarrhoea and oesophagitis with CRT Path CR: 29% vs. 3% for CRT vs. CT ($p < 0.01$) Significant nodal downstaging: 77% vs. 35% for CRT vs. CT ($p < 0.01$) Post-operative complications: anastomotic leak – 7% in CRT group and 0% in CT group ($p = 0.03$) Atrial fibrillation – CRT vs. CT 18% vs. 5% ($p = 0.0012$) Pulmonary insufficiency – 15% vs. 3% ($p = 0.007$) Hospital Mortality: CRT 7% vs. CT 4% $p = 0.4$	CT trials took place between 1990 and 1995. Patients were recruited into CRT trials between 1996 and 2000. 90% of CRT patients proceeded to surgery vs. 75% in CT group ($p = 0.04$). Median follow-up 190 months for CT and 93 months for CRT. Improvement in survival with CRT seen even if follow-up had ended in 2000 ($p = 0.005$). As a result of the number of trials, there was wide heterogeneity in the treatment patients received, and four different regimens were used.
Morgan, 2007, Wales[5]	205 patients with cT3, N0–N1 M0 AC or SCC of the oesophagus between 1998 and 2005 CT: ($n = 88$) CRT: ($n = 117$)	Non-randomised, non-blinded cross-over trial (III)	CT: either 2 cycles of cisplatin (80 mg/m^2) + 5-FU (1000 mg/m2), or epirubicin (50 mg/m^2), cisplatin (60 mg/m^2) + 5-FU (200 mg/m^2) CRT: 2 cycles of cisplatin (60 mg/m^2) + 5-FU (225 mg/m^2 daily) followed by 45 Gy radiotherapy in 25 fractions + cisplatin + 5-FU.	OS: Median survival 28 vs. 22 months for CRT vs. CT 5 year survival 35% vs. 21% in the CRT vs. CT groups ($p = 0.188$) (on intention to treat basis) Toxicity: Grade IV neutropaenia 25% in CRT group vs. 0% for CT group Path CR: 18% vs. 3.4% in the CRT vs. CT groups ($p = 0.012$) R0: 64.8% in CRT group 47.0% in CT group ($p = 0.009$)	From 1998 patients received CRT, then from 2002 onwards they received CT. Of CRT patients, 91% were followed up for 5 years. Of CT patients 59.8% were followed up for 5 years. 24% of patients in the CRT group and 19% in the CT group did not progress to surgery. However, 12% of patients in the CT group had an open close laparotomy vs. 5% in the CRT group.

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Table 1 (*continued*)

Author, date and country	Patient group	Study type (level of evidence)	Regimen	Key outcomes	Comments
Luu, 2008, USA[6]	122 patients with Stage II – stage IV AC or SCC of the oesophagus between 1995 and 2005 CT: ($n = 58$) CRT: ($n = 64$)	Retrospective, cohort study (III)	CT: 6 different regimens used involving carboplatin, cisplatin, 5-FU, taxol, Etoposide and leucovorin CRT: also variable, ranging from 45 to 60 Gy in total	Peri-operative mortality: 10% in the CRT group vs. 1% for the CT group ($p = 0.008$) OS: 1-, 3- and 5-year survival after CT 70, 40 and 31% 1-, 3- and 5-year survival after CRT was 76%, 46%, and 41% ($p = 0.305$) Toxicity: Not analysed Path CR: 17% after CRT, 3% after CT ($p = 0.02$) R1 resection: 8% after CRT and 9% after CT ($p = 1.00$) Overall complication rate: 48% after CRT and 33% after CT ($p = 0.09$) Operative mortality 6% in CRT group and 0% in CT group ($p = 0.12$) DFS: Median 15.8 months after CT vs. 13.7 months after CRT ($p = 0.02$)	Surgery not standardised but single institution. 95% in CT and 97% in CRT had Ivor Lewis. Initially looked at all oesophagectomy patients. 97% of patients who had planned CT/CRT and surgery completed their treatment. Median length of follow-up and range not reported.

AC: adenocarcinoma; SCC: squamous cell carcinoma; Path CR: pathological complete response; CT: chemotherapy; CRT: chemoradiotherapy; RT: radiotherapy; DFS: disease free survival; OS: overall survival.

directly compared the results of neoadjuvant CT to CRT were assessed in detail.

5. Search outcome

1115 papers were found using the described search technique and abstracts were searched. Of these, 1110 papers did not address the primary question and directly compare CRT to CT and therefore were discarded. Five papers were identified that provided the best evidence to answer the clinical question. These are presented in Table 1.

6. Results

There were 2 randomised controlled trials (level II), 2 prospective series (level II) and a retrospective study (level III) which were found to be directly relevant to the research question.

The first RCT published by Stahl et al. in 2009 recruited 119 patients with locally advanced adenocarcinoma (T3–T4, NX, M0).[3] The patients were recruited between 2000 and 2005 from 19 different hospitals in Germany. In the CT group, only 66% completed the course, and one patient died of toxicity. Seventy-five percent of patients completed CRT. The percentage of patients who proceeded to surgery after neoadjuvant treatment was 88% and 82% in the CT group and CRT groups, respectively. Complete pathological response was significantly higher in the CRT group (15%) compared with CT group (2%) ($p = 0.03$). The R0 resection rate was also increased with CRT in those who had surgery, however given the excess number of patients who did not proceed to surgery in the CRT group there was no difference on an intention to treat analysis. The improvement in 3-year survival data failed to reach significance ($p = 0.07$). After the first 125 patients were recruited, an interim analysis revealed that another 163 patients would be required for each arm to show an improvement in 3-year survival by 10% (with 80% power) for the CRT arm. Therefore, less than a third of the required number of patients had been recruited in the first 5 years, prompting early closure of the trial. Other criticisms of this RCT include a low dose of radiotherapy (30 Gy) and the CT regimen was prolonged with non-conventional schedule of induction and concurrent treatment schedule.

The second RCT was published by Burmeister et al. in 2011.[4] This trial randomised 75 patients with adenocarcinoma of the thoracic oesophagus or gastro-oesophageal junction with T2–T3, N0–N1, M0 disease. There was no difference in toxicity due to neoadjuvant therapy between the two arms. This study again showed an improvement in the pathological response rate after CRT (13% vs. 0% in the CT group ($p = 0.02$)) and there was a higher rate of R1 resection in the CT group (11% vs. 0% ($p = 0.04$)). However, a higher percentage of patients in the CT group proceeded to surgery (92% vs. 85% in the CRT group). Therefore, there was no improvement in R0 resection on an intention to treat basis. Five-year survival after CRT was 45% vs. 36% for the CT group, but this was not statistically significant ($p = 0.6$). Again, this trial was closed early due to poor accruals and long waiting times for radiotherapy.

In 2010, Swisher et al. published a re-analysis of the outcomes of 157 patients that had been randomised to sequential phase II and phase III studies of pre-operative CT or CRT.[5] The data was collected from a single centre, between 1990 and 2005. 85% of patients had adenocarcinoma, and the majority had T2–3, N0–1, M0 disease. There was a higher incidence of grade III and grade IV toxicity with CRT compared to CT. In contrast to the two RCT previously discussed, there was a significantly higher number of patients in the CRT group who proceeded to surgery compared to the CT group (90% vs. 75%, respectively ($p = 0.04$)). There was no difference in peri-operative mortality, but there was a higher incidence of post-

operative morbidity in the CRT group. Again, there was improvement in the pathological response rate after CRT (29% vs. 3% in the CT group) and there was a significant improvement in 5-year survival seen (36% of the CRT alive at 5 years vs. 21% of the CT group calculated on an intention to treat basis ($p = 0.04$)). Major criticisms of this research include that data from four different trials were used in this analysis. In addition, the four trials were sequential and spanned 10 years. Pre-treatment staging changed over this time and the lack of endoscopic ultrasound and PET imaging earlier in the study may have not excluded patients with advanced or metastatic disease. CT trials took place between 1990 and 1995. Patients were recruited into CRT trials between 1996 and 2000. Furthermore, two different types of oesophagectomy were used. However, it was an intention to treat analysis and did use high quality data from randomised studies.

Morgan et al. performed a prospective cohort study of 205 patients with oesophageal cancer who underwent neoadjuvant therapy followed by surgery.[6] The first cohort, from 1998 to 2002, received CRT, whereas between 2002 and 2005 CT was used. The patients were well staged with EUS, helical CT and staging laparoscopy, but not PET scanning. The CRT patients were younger compared to the CT group. Eighty three percent in the CT group had adenocarcinoma compared with 70% in the CRT group. The complete pathological response rate was higher after CRT (18% vs. 3.4% in the CT group ($p = 0.012$)). The 5-year survival was not statistically significant (35% 5 year survival following CRT vs. 21% in the CT group, $p = 0.188$). However, 24% of patients in the CRT group and 19% in the CT group did not progress to surgery. Peri-operative mortality was higher in the CRT group (10% vs. 1% for the CT group ($p = 0.008$)), but open–close laparotomy was higher in the CT group (12% vs. 5% in the CRT group, $p = 0.044$).

Luu et al. performed a retrospective study published in 2008 involving 122 patients who underwent neoadjuvant treatment at a single centre between 1995 and 2005 for stage II to stage IV disease.[7] Seventy six percent of the CT group had adenocarcinoma compared with 81% in the CRT group. Ninety seven percent of the patients in both groups completed all planned neoadjuvant treatment and proceeded to surgery. Peri-operative complications were higher in the CRT group with four peri-operative deaths and an overall complication rate of 48% compared to 33% overall complication rate in the CT group ($p = 0.09$). Consistent with the other studies, there was improvement in the pathological complete response rate after CRT (17% vs. 3% in the CT group ($p = 0.02$)). The 5-year survival after CRT was 41% vs. 31% for the CT group, but this result did not reach statistical significance. The main criticisms of this study were that it was retrospective and the pre-treatment stage was not accurately known. Survival was calculated from the date of oesophagectomy and not the date of commencing neoadjuvant therapy.

7. Clinical bottom line

The current literature comparing neoadjuvant CRT vs. CT prior to oesophagectomy for cancer is limited, in particular the randomised trials which were underpowered and closed early. The studies presented here suggest that CRT increases the pathological complete response rate and may be associated with a survival advantage. However, this is at the cost of increased peri-operative morbidity and mortality that may offset the survival gain. Two high quality randomised controlled trials have recently started recruiting and are comparing different neoadjuvant CT and CRT regimens (MAGIC vs. CROSS [NCT01726452, ClinicalTrials.gov] and Neoscope[8]) and should clarify the existing deficits in the literature.

Ethical approval

Ethical approval was not sought.

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Author contribution

EH, RV and EG were all involved in the medline search, screening of abstracts, analysis of papers and the writing process.

Conflict of interest

I declare there are no conflicts of interest from any authors on the paper.

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